Thermo- and pH-Responsive Behavior of Poly(*N*-isopropylacrylamide)-Block-Poly[(2-dimethylamino)ethyl Methacrylate]

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Abstract: *The influence of poly(2-dimethylamino)ethyl methacrylate (PDMAEMA) block on the thermo- and pH-responsive behavior of poly(N-isopropyl acrylamide)-block-poly[(2-dimethylamino)ethyl methacrylate)] (PNIPAM-b-PDMAEMA) was studied. The block copolymers were synthesized using reversible addition-fragmentation chain transfer (RAFT) polymerization by varying the chain length of the second block (PDMAEMA). ^{1}H-NMR and FTIR spectra confirmed the formation of block copolymers PNIPAM$_{21}$-b-PDMAEMA$_2$ and PNIPAM$_{21}$-b-PDMAEMA$_7$ with the corresponding molar masses from the GPC data. Thermo- and pH-responsive behavior of block copolymers was investigated in phosphate buffer with various pHs. Interesting results showed that the hydrophilic carboxyl end group and the hydrophobic dodecyl end group of the RAFT agent affected the resulting phase transition temperature (T_c), while the T_c was found to be low in the acidic environment. Moreover, larger particle sizes of PNIPAM$_{21}$-b-PDMAEMA$_2$ were found with a pH of 9. It is noteworthy, that the resulted block copolymers might have the potential use in a drug delivery system.*

Keywords: *block copolymer; PNIPAM; PDMAEMA; thermo-responsive polymers; pH-responsive polymers*

■ INTRODUCTION

Stimulus-responsive polymers can undergo reversible changes in properties in the solution when external stimuli are applied, such as pH, temperature, and chemical and biological agents. The combination of two or more different monomers that have a different response to a stimulus can result in multi-responsive copolymers [1]. In particular, temperature and pH are interesting stimuli that can be explored, including their applications [2-6] due to their availability in the environment.

Two types of thermo-responsive behavior for polymers are lower critical solution temperature (LCST) and upper critical solution temperature (UCST). In LCST-type polymers, the polymers are soluble at the temperature range below their phase transition temperature (T_c), otherwise, a soluble-to-insoluble happens while heating. Vice-versa, UCST-type polymers are soluble above T_c. An example of a widely used LCST-type polymer is poly(*N*-isopropyl acrylamide) (PNIPAM)

with a T_c of 32 °C [7].

In addition to temperature, another external stimulus that is widely used in the field of responsive polymers is pH. There are two types of pH-responsive polymers, i.e., polymers with acidic groups (poly acids) and basic groups (poly bases) [1]. Deprotonation of acidic groups within the chain of poly acids results in a negative charge at high pH and causes the polymer to become more hydrophilic. Conversely, the basic group in polybasic is protonated at low pH and increases its solubility in water media as in the case of poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA) [7].

Research concerning thermo- and/ or pH-responsive block copolymers has been widely developed recently [8-9], especially in drug delivery systems due to the reversible solubility of thermo-responsive blocks [10] and reversible ionization of pH-responsive blocks [11]. The idea is to use both properties to promote self-assembly and form micelles because of the changes in

hydrophobic-hydrophilic properties, in which the hydrophobic drugs can be loaded in the core of the micelles and then released when the micelles deform to unimers.

Thermo- and pH-responsive block copolymers can be synthesized using one block that has thermo-responsive behavior, and the other block that consists of a pH-responsive polymer [1]. One possible way to synthesize such block copolymers is by using controlled radical polymerization, namely reversible addition-fragmentation chain transfer (RAFT). Several studies on the use of RAFT to synthesize multi-responsive block copolymers have been reported, not only for diblock [12] but also for triblock copolymers [13-15].

Herein we report our studies about the synthesis of block copolymers of PNIPAM-b-PDMAEMA via RAFT by varying the chain length of the second block of PDMAEMA and investigating their thermo- and pH-responsive behavior. 2-(Dodecylthiocarbonothioylthio)-2-methyl propionic acid (DDMAT) was used as a chain transfer agent, which hypothetically might also influence the pH-responsive behavior of the resulted block copolymers due to the presence of carboxyl groups [16-17]. The copolymers were constructed by forming PNIPAM as the macro-CTA first and followed by the addition of DMAEMA as the second block. To our knowledge, the thermo- and pH-responsive behavior of PNIPAM-*b*-PDMAEMA has not been studied yet.

■ EXPERIMENTAL SECTION

Materials

The materials used in this study were N-isopropylacrylamide (NIPAM, 97% purity, Sigma-Aldrich), 2-(dimethylamino)ethyl methacrylate (DMAEMA, 98% purity, Sigma-Aldrich), 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid (DDMAT, 98% purity, Sigma-Aldrich). 1,4-dioxane was obtained from Smart-Lab. 2,2′-azobisisobutyronitrile (AIBN, 98% purity, Clariant), potassium dihydrogen phosphate (KH_2PO_4, 99% purity, Merck) and dipotassium hydrogen phosphate (K_2HPO_4, 99% purity, Merck). Sodium hydroxide (NaOH) and phosphoric acid (H_3PO_4) were obtained from Rofa Laboratorium Centre.

Instrumentation

The instrumentations used in this study were Fourier transform infrared (Shimadzu-IR Prestige 21) and proton magnetic resonance (Bruker Advance 500 MHz) to characterize the chemical structure of the block copolymers. Gel permeation chromatography (Shimadzu LC-20 equipped with column LF 804) was used for molecular weight determination of the block copolymers. Thermo- and pH-responsive behavior was investigated using UV-Visible spectrophotometer (Thermo Scientific Multiscan Go UV-Visible spectrophotometer) and particle size analyzer (Horiba SZ 100z Nano Particle Size Analyzer).

Procedure

Synthesis of PNIPAM macro-CTA

NIPAM monomer (2.8326 g, 25 mmol) and DDMAT (0.2572 g, 0.7 mmol) were dissolved in 5 mL 1,4-dioxane and put into a Schlenk flask equipped with a magnetic bar. The solution was degassed with nitrogen under stirring for 15 min, and the flask was placed in a preheated oil bath at 70 °C. After that, AIBN (0.02 g, 0.12 mmol), which was pre-dissolved in 2.5 mL 1,4-dioxane, was rapidly transferred into the Schlenk flask. Polymerization was carried out for 6 h at 70 °C under stirring. The polymerization reaction was quenched by placing the flask in an ice bath and exposing the solution to air. PNIPAM was isolated by three cycles of precipitation-decantation in cold *n*-hexane and then dried in an oven at 60 °C overnight to obtain yellow powder (2.1746 g, 69.92% yield). The synthesis procedure was adapted from the work of Giaouzi and Pispas [12].

Synthesis of PNIPAM-b-PDMAEMA block copolymers

PNIPAM was used as macro-CTA to produce PNIPAM-*b*-PDMAEMA block copolymers with the ratio that can be seen in Table 1. The synthesis procedure are as follows: DMAEMA (0.5830 g, 3.7 mmol), PNIPAM macro-CTA (0.4378 g, 0.16 mmol), and 5 mL 1,4-dioxane were added into a 25 mL Schlenk flask equipped with a magnetic bar. Oxygen was removed from the solution by bubbling with nitrogen for 15 min under stirring, and then the flask was placed in a preheated oil

Table 1. Recipe for the synthesis of PNIPAM-*b*-PDMAEMA

Product	NIPAM (g)	DMAEMA (g)	DDMAT (g)	Macro-CTA (g)	AIBN (g)
PNIPAM Macro-CTA	2.8326	-	0.2572	-	0.02
PNIPAM$_{21}$-*b*-PDMAEMA$_2$	-	0.5830	-	0.4378	0.0045
PNIPAM$_{21}$-*b*-PDMAEMA$_7$	-	0.7751	-	0.6077	0.0030

Note: Reaction occurred for 6 h at 70 °C

oil bath at 70 °C. Then, AIBN (0.0045 g, 0.03 mmol) in 2.5 mL 1,4-dioxane was added into a Schlenk flask. Polymerization was carried out at 70 °C with continuous stirring for 6 h and stopped by quenching it in an ice bath and exposing it to air. The polymerization product was obtained by three cycles of precipitation-decantation in cold *n*-hexane and then dried in an oven at 60 °C overnight. The synthesis method was adapted from the work of Giaouzi and Pispas and Tebaldi et al. with modifications [12,18].

■ RESULTS AND DISCUSSION

Synthesis and Characterization of PNIPAM-*b*-PDMAEMA Block Copolymers

PNIPAM$_{21}$ was used as the macro-chain transfer agent for the subsequent RAFT polymerization of DMAEMA to obtain PNIPAM-*b*-PDMAEMA block copolymers. The PNIPAM-*b*-PDMAEMA was synthesized by varying different chain lengths of PDMAEMA, and each polymer was characterized by FTIR, ^{1}H-NMR, and GPC analysis. The synthetic route followed is depicted in Scheme 1. Fig. 1 shows the FTIR spectra of NIPAM, PNIPAM macro-CTA, and PNIPAM-*b*-PDMAEMA block copolymers. By comparing each of the spectra, some differences can be noticed, which indicate that a new compound has been formed. FTIR spectra of PNIPAM macro-CTA and PNIPAM-*b*-PDMAEMA showed no C=C peak at 1600–1650 cm^{-1} [19], suggesting that polymerization has occurred [20]. Meanwhile, in the FTIR spectra of PNIPAM macro-CTA and PNIPAM-*b*-PDMAEMA, there were peaks at 3076 and 3075 cm^{-1}, respectively, which could be attributed to the stretching vibration of C(sp^2)-H group but the intensity of the peak was lower in
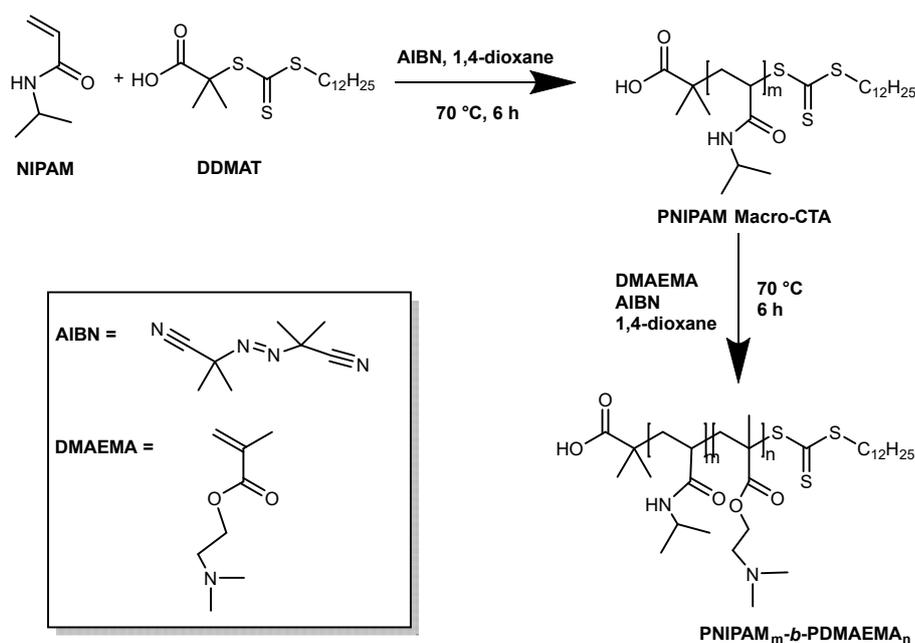
**Scheme 1.** Synthetic route of PNIPAM-*b*-PDMAEMA block copolymers
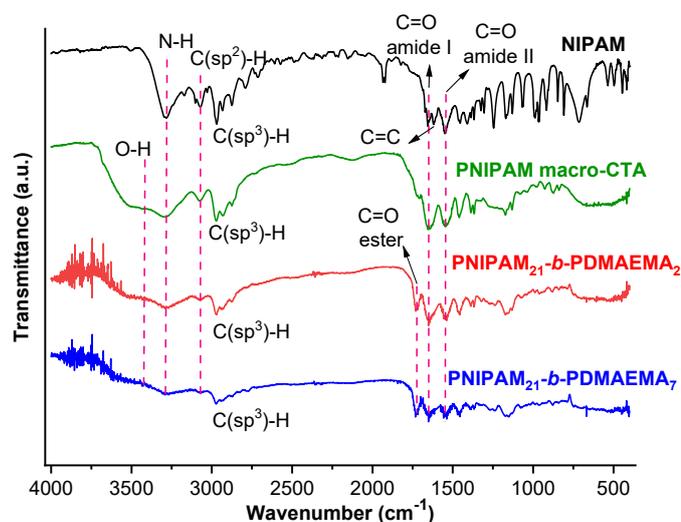
Fig 1. FTIR spectra of NIPAM, PNIPAM macro-CTA, and PNIPAM-*b*-PDMAEMA

comparison with NIPAM, confirming that some unreacted monomer still existed. Compared with the FTIR spectrum of PNIPAM macro-CTA, a peak at 1728 cm^{-1} appeared in the FTIR spectra of PNIPAM-*b*-PDMAEMA after copolymerization, indicating the presence of C=O ester from the PDMAEMA block. Characteristic peaks of PNIPAM in FTIR spectra of PNIPAM-*b*-PDMAEMA can be observed, as evidenced by the presence of the peak at 3288 cm^{-1} that was ascribed to N-H stretching vibration, while the peak at 1647 cm^{-1}

was ascribed to C=O amide I and the peak at 1544 cm^{-1} was assigned to C=O amide II. The absorption peak at 3436 cm^{-1} was a stretching vibration of O-H in the COOH end group.

^{1}H-NMR spectra of PNIPAM macro-CTA and PNIPAM-*b*-PDMAEMA block copolymers in CDCl$_3$ are shown in Fig. 2. Based on the resulting FTIR spectra, there was a peak of C(sp^2)-H group in the products, which also occurred in the ^{1}H-NMR spectra. In this study, one of the peaks of three protons from the vinyl group of PNIPAM was detected at 5.5 ppm, confirming that there were still some NIPAM monomer impurities remaining in the product (Fig. 2(a)). Fig. 2(b) and 2(c) show that peaks of DMAEMA monomer were still detected, which were attributed to peak o, p, and q. These results were similar to the results obtained by De Jesús-Téllez et al. when characterizing the DMAEMA monomer [21], suggesting that there was still unreacted DMAEMA monomer in the copolymer product and the purification process has not been optimal. This happened most probably due to the non-polar properties of *n*-hexane that makes the immersion of the product in *n*-hexane needs to be longer before decantation to allow the monomers to be more soluble in *n*-hexane. Previous work from Göktaş in 2020 reported similar results of the existence of the vinyl peak
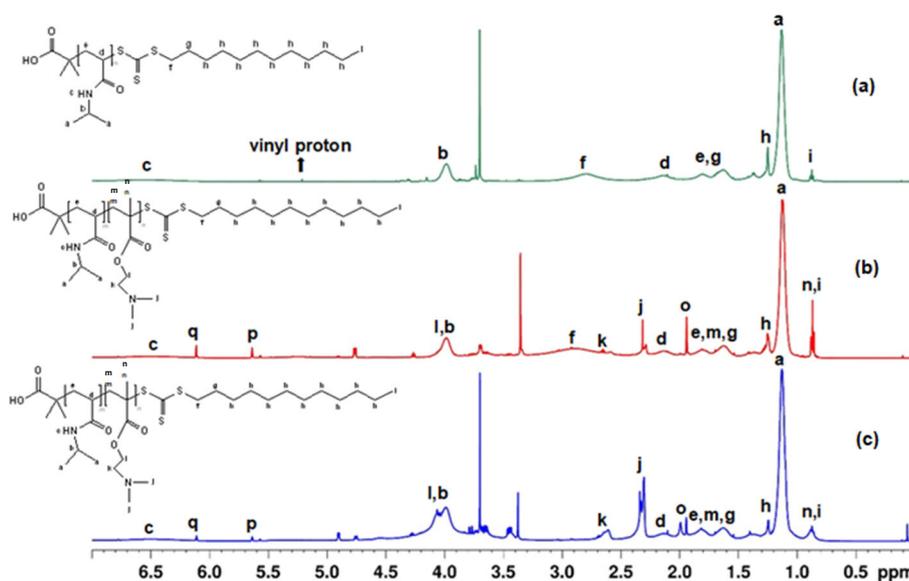
Fig 2. ^{1}H-NMR spectra of PNIPAM macro-CTA (a), PNIPAM$_{21}$-*b*-PDMAEMA$_2$ (b), and PNIPAM$_{21}$-*b*-PDMAEMA$_7$ (c) in CDCl$_3$

from the DMAEMA monomer when the purification was performed using methanol as the precipitation medium [22].

Based on Fig. 2(a), it is shown that PNIPAM macro-CTA was successfully synthesized, indicated by the presence of characteristic peaks a 1.12 ppm (-CH(CH$_3$)$_2$, 6H) and b 3.98 ppm (-CH(CH$_3$)$_2$, 1H) which were similar to the previous study [23]. By calculating the ratio of the integrated peak areas between peak b from PNIPAM and peak i from the dodecyl end group, the repeating unit of PNIPAM was found to be about 21 and the molecular weight (M$_n$) was at 2728 g/mol.

As displayed in Fig. 2(b) and 2(c), some new peaks appeared in the ^{1}H-NMR spectra of PNIPAM-*b*-PDMAEMA in comparison with the ^{1}H-NMR spectrum of PNIPAM macro-CTA. Characteristic peaks of PDMAEMA were assigned to peak j, k, l, and n. Overlapping double peaks around 4 ppm were ascribed to the proton of -CH(CH$_3$)$_2$ from the PNIPAM block (peak b) and the proton of -CH$_2$CH$_2$N(CH$_3$)$_2$ from the PDMAEMA block (peak l). Peak f of the dodecyl end group did not always appear in every ^{1}H-NMR spectrum of the PNIPAM-*b*-PDMAEMA block copolymers, as reported in a previous study [24].

The repeating unit of PDMAEMA in the copolymers was determined by comparing the integration of the protons j and a, which was found to be 2 with molecular weight (M$_n$) at 3043 g/mol (Fig. 2(b)). Meanwhile, as seen in Fig. 2(c), the molecular weight (M$_n$) at 3829 g/mol and degree polymerization (DP) at 7 were calculated from integral values of peak areas of the signals k and a.

The molecular weight characterization was performed by gel permeation chromatography (GPC) using THF as eluent and polystyrene as the standard (Table 2). Analysis of PNIPAM macro-CTA using GPC resulted in narrow molecular weight distribution with tailing at the lower molecular weight side (Fig. 3). The presence of the tailing was probably due to the presence of residual impurities in the final product, such as chain transfer agent (CTA) [25].

Different from PNIPAM macro-CTA, GPC traces of block copolymers were relatively symmetric and showed no tailing at the lower molecular side (Fig. 3). Higher retention time was observed in the comparison of PNIPAM$_{21}$-*b*-PDMAEMA$_2$ with PNIPAM$_{21}$-*b*-PDMAEMA$_7$ suggesting that the resulting M$_n$ were increased from 1860 to 1923 g/mol which was ascribed to PNIPAM$_{21}$-*b*-PDMAEMA$_2$ and PNIPAM$_{21}$-*b*-PDMAEMA$_7$, respectively. Whereas the unexpected increase in retention time of both block copolymers in comparison with PNIPAM macro-CTA was observed, indicating that the molecular weight (M$_n$) decreases in
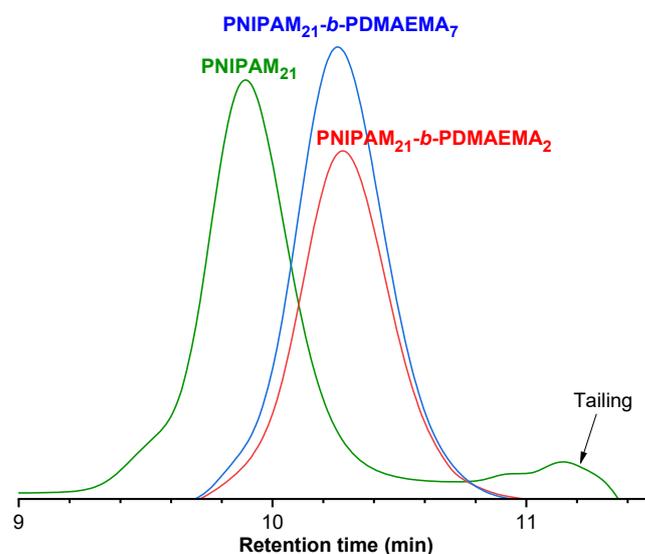
Fig 3. GPC traces of PNIPAM macro-CTA, PNIPAM$_{21}$-*b*-PDMAEMA$_2$, and PNIPAM$_{21}$-*b*-PDMAEMA$_7$

Table 2. Molecular characterization of block copolymers and macro-CTA

No	Sample	M$_n$[a] (g/mol)	M$_n$[b] (g/mol)	M$_w$/M$_n$[c]
1	PNIPAM$_{21}$	2728	3475	1.15
2	PNIPAM$_{21}$-*b*-PDMAEMA$_2$	3043	1860	1.10
3	PNIPAM$_{21}$-*b*-PDMAEMA$_7$	3829	1923	1.10

The degree of polymerization was estimated by ^{1}H-NMR analysis. [a] The molecular weight by ^{1}H-NMR analysis. [b] The molecular weight by GPC analysis. [c] The Polydispersity index (PDI) or M$_w$/M$_n$ values determined by GPC analysis

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contrast to the ^{1}H-NMR result (Table 2). In GPC analysis, the sample must first dissolve in a solvent; once they have been dissolved, the molecules will change their conformation from long chains to coil conformation. These coiled-up polymers in the mobile phase would then flow into the GPC column. If polymer coils are larger than the pores, they do not enter the pores and need lower retention time, but small polymer coils can enter the pores and will take more time to pass the column. In other words, the retention time decreases when the hydrodynamic radius of the polymer is larger [26]. In this study, the interaction between PNIPAM and PDMAEMA block in polar THF, such as hydrophobic interaction and hydrogen bonding, might lead to reducing the size of hydrodynamic diameter and an increase in retention time. The previous study also reported unusual results on the retention time of PNIPAM-*b*-PPEGA block copolymer, which was higher than the initial PNIPAM due to intense interaction between PNIPAM and PPEGA via hydrogen bonding, indicating that the hydrodynamic volume of the block copolymer was smaller than the initial PNIPAM that could be attributed to higher retention time [27].

We also tried to synthesize PNIPAM-*b*-PDMAEMA block copolymers with a longer targeted PDMAEMA chain than PNIPAM, but it did not succeed, which might be due to the effect of the R group (C(CH₃)₂COOH) from CTA on the DMAEMA monomer which caused the intermediate radical fragmentation to become a dormant chain and R• took place slowly, where it was known that R• plays a role in reinitiating the polymerization reaction [28].

Thermo-Responsive Properties of PNIPAM-*b*-PDMAEMA Block Copolymers

PNIPAM is a thermo-responsive polymer with LCST-type behavior that undergoes a soluble-to-insoluble phase change upon heating. The phase transition temperature is the temperature at which the phase transition of the polymer solution at a specific concentration occurs from a soluble state to a collapsed state to form aggregates accompanied by the appearance of turbidity in the solution [29]. Meanwhile, LCST is the minimum temperature at the binodal where the phase change occurs [30]. Above the LCST, there is a tendency for the microphase separation rather than the macro phase separation to produce nano aggregates from polymers. Therefore, the phase transition temperature (T_c) is usually detected by an increase in the turbidity of the polymer solution [16]. It is widely known that PNIPAM has a T_c of 32 °C [7], independently of its molecular weight and concentration. The phase transition temperature of PNIPAM can be adjusted to a higher or lower temperature, one of which is by the addition of comonomers where water-soluble comonomers will increase the T_c, while hydrophobic comonomers will decrease T_c. In addition, the presence of the end group might also affect the shift in the T_c value of PNIPAM. A previous study reported that the end group derived from azo initiators such as AIBN is known to have minimal effect on T_c, whereas water-soluble end groups such as -OH and -NH₂ tend to increase T_c and the hydrophobic end groups influence decreasing T_c [30]. It was expected that by adding comonomer of DMAEMA, T_c of PNIPAM-*b*-PDMAEMA would increase in comparison with its macro-CTA, PNIPAM itself.

As shown in Fig. 4, PNIPAM₂₁ does not show a significant change in transmittance at a temperature range of 15–45 °C and begins to experience a decrease in transmittance when the temperature is above 45 °C. This
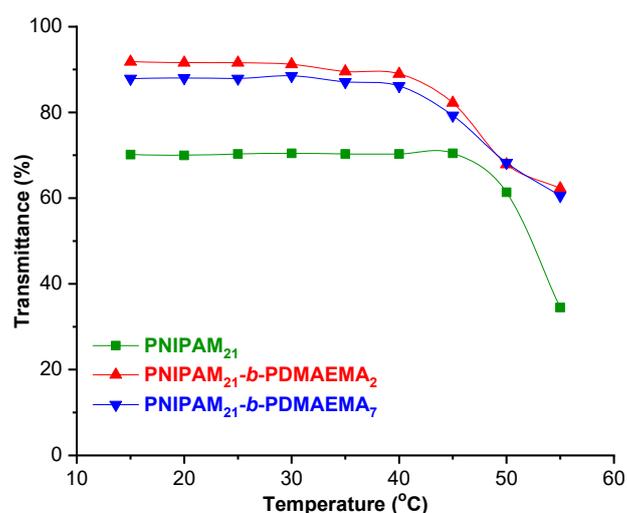
Fig 4. Thermo-responsive behavior of PNIPAM-*b*-PDMAEMA in pH 7.4 at a concentration of 1 g/L

behavior could be reasoned because at pH 7.4, the thermo-responsive behavior of PNIPAM$_{21}$ was influenced by the hydrophilic end group -COOH, which was ionized to -COO$^-$ at alkaline pH, and thus the T$_c$ shifted to a higher temperature of 52 °C. Below the T$_c$, the amide group of PNIPAM can form hydrogen bonding with water molecules in the solution and become transparent. In the case of an increase in temperature above the T$_c$, the hydrogen bonds are weakened so that the hydrophobic interaction between the hydrophobic backbone and the isopropyl group of PNIPAM becomes dominant, in which the interactions lead to aggregation [31].

Furthermore, in block copolymers PNIPAM$_{21}$-*b*-PDMAEMA$_2$ and PNIPAM$_{21}$-*b*-PDMAEMA$_7$, there was a significant decrease of transmittance at temperatures above 40 °C as displayed in Fig. 4, and the same values of T$_c$ were obtained for each copolymer which was about 47 °C. The T$_c$ of the PNIPAM-*b*-PDMAEMA block copolymers shifted to a lower temperature in comparison with the T$_c$ of the PNIPAM$_{21}$ macro-CTA (52 °C). At first, it was predicted that there would be an increase in hydrophilicity of the block copolymers in the higher pH since PDMAEMA is partially protonated on its tertiary amino group at pH 7.4 and become positively charged. However, an opposite trend of decreased T$_c$ was observed,

which might be due to the hydrophobic interaction from the dodecyl end group from the chain transfer agent and the carboxyl group in the protonated form .

As displayed in Scheme 2, above the T$_c$, hydrophobic interaction becomes dominant, and the solution appears cloudy, which shows that the block copolymers exhibit LCST behavior. These might also indicate the formation of a micelle with a PNIPAM block and dodecyl end group occupying the core of the micelle and a PDMAEMA block with a COOH end group constituting the hydrophilic shell of the micelle.

pH-Responsive Properties of PNIPAM-*b*-PDMAEMA Block Copolymers

Fig. 5 shows the pH-responsiveness of PNIPAM macro-CTA and PNIPAM-*b*-PDMAEMA block copolymers in a phosphate buffer solution. In general, PNIPAM is not a pH-responsive polymer, but based on the observations using UV-Vis spectrophotometer in phosphate buffer at pH 5, 7.4, and 9, it was observed that there was a pH-responsive behavior from PNIPAM macro-CTA, indicated by the difference in the resulting T$_c$. At pH 5, PNIPAM$_{21}$ produces a T$_c$ of 27 °C, lower than the T$_c$ of PNIPAM in general, which is 32 °C. This is because of the dodecyl end group, which is closely attached to the PNIPAM block. The dodecyl group is
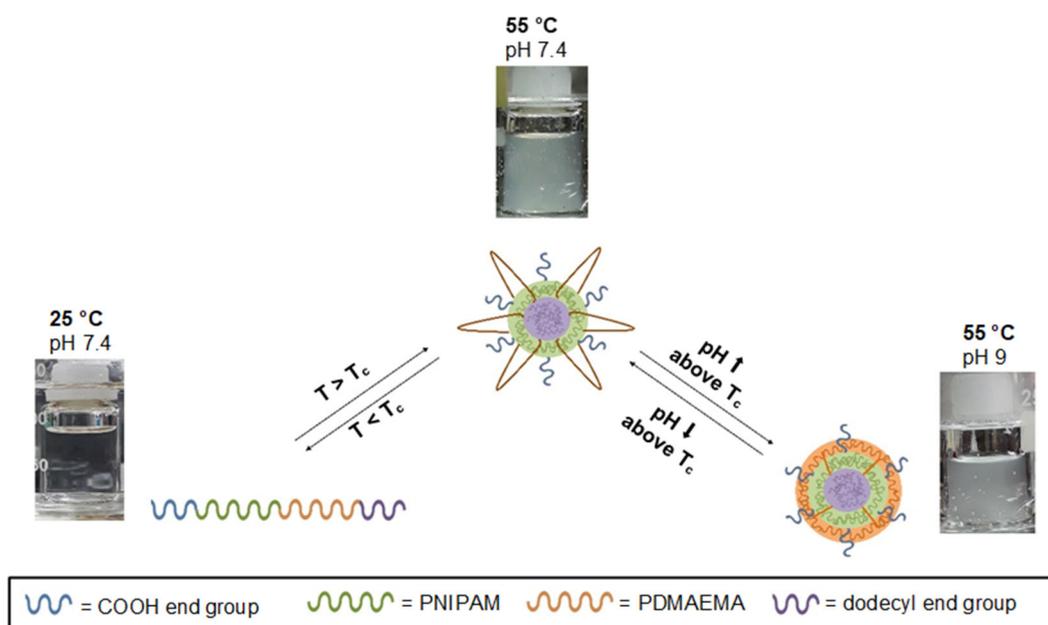
Scheme 2. Proposed illustration of self-assembly behavior of PNIPAM-*b*-PDMAEMA
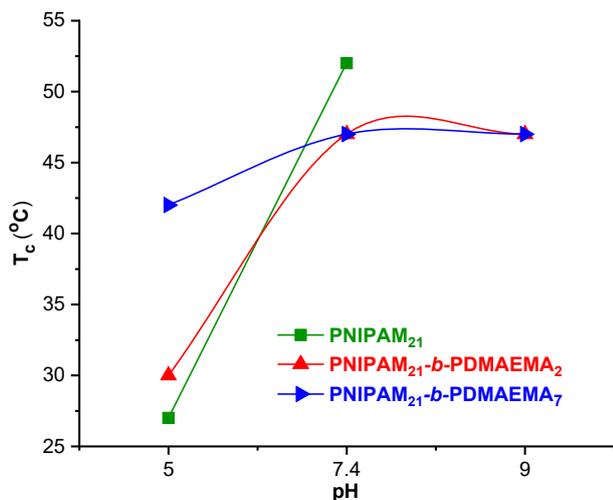
Fig 5. Effect of pH on the resulting T_c of 1 g/L PNIPAM-*b*-PDMAEMA and PNIPAM macro-CTA

known to be hydrophobic, which will increase the hydrophobic effect of the PNIPAM macro-CTA, resulting in a cloud point that can be achieved at a lower temperature. A similar phenomenon also occurred in the previous study [12].

Based on the graph in Fig. 5, it is shown that there was a drastic increase in the T_c of PNIPAM macro-CTA reaching 52 °C at pH 7.4, which was due to the increase in solubility of PNIPAM macro-CTA at pH 7.4, caused by the presence of the -COOH group in the macro-CTA PNIPAM. It was known that when -COOH was dissolved in an alkaline solution, deprotonation of COOH into COO⁻ occurred, and thus, the solubility of PNIPAM macro-CTA increased. Meanwhile, increasing the pH to 9 showed that the T_c of macro-CTA PNIPAM was not observed at temperature measurement. This was probably due to the increase in hydrophilicity that also increased the T_c. A similar result was observed in the research conducted by FitzGerald et al. when observing surfactant PNIPAM, which had the same dodecyl and carboxyl end groups [17].

The effect of the PDMAEMA chain length on the PNIPAM-*b*-PDMAEMA block copolymer on pH was observed using a UV-Vis spectrophotometer. PDMAEMA is a pH-responsive polymer of the polybasic type which will be protonated at low pH (pH < pKa 7.5) [32]. Hence, the solubility of PDMAEMA in an acidic pH buffer solution increase, causing the hydrophilic effect of

PDMAEMA to be more dominant, accompanied by an increase in T_c. As shown in Fig. 5, at pH 5, PNIPAM$_{21}$-*b*-PDMAEMA$_2$ and PNIPAM$_{21}$-*b*-PDMAEMA$_7$ obtained T_c values of 30 and 42 °C, respectively, higher values in comparison to macro-CTA PNIPAM$_{21}$ (27 °C. The increase in T_c was due to the presence of PDMAEMA, which was protonated at pH 5, which attributed in affecting the changes in the hydrophilic-to-hydrophobic properties of its neighboring block PNIPAM due to weakening of the hydrophobic aggregation force in PNIPAM [14]. Above the T_c, PNIPAM-*b*-PDMAEMA self-assembled into nanostructures consisting of PNIPAM block and dodecyl end group as micelle core and PDMAEMA block with COOH end group as micelle shell (Scheme 2). Moreover, at pH 5, T_c increased the degree of polymerization of the PDMAEMA block due to the greater effect of the hydrophilicity of protonated PDMAEMA in the PNIPAM-*b*-PDMAEMA block copolymers.

When pH increased to 7.4, it was expected that increasing pH would cause the T_c of block copolymers to be reduced because the degree of protonation in PDMAEMA was much lower than that at pH 5. On the contrary, the T_c of PNIPAM$_{21}$-*b*-PDMAEMA$_2$ and PNIPAM$_{21}$-*b*-PDMAEMA$_7$ at pH 7.4 were increased from the previous pH, which could be reasoned by the existence of deprotonated COOH groups into COO⁻, leading to increased solubility of block copolymers in dispersing media and also increased T_c. Other than that, at pH 7.4, the T_c of block copolymers was lower than the T_c of PNIPAM macro-CTA (52 °C), in which the T_c values were similar for both block copolymers at approximately 47 °C (Fig. 5). The decrease in T_c in comparison with T_c PNIPAM macro-CTA might be contributed by the presence of PDMAEMA. At pH 7.4 it was known that PDMAEMA was in the protonated state, but the degree of protonation was lower than that at acidic pH. This resulted in the possibility of hydrophobic interactions between the PNIPAM block and the PDMAEMA block when the temperature increased.

PDMAEMA was deprotonated at pH 9. The resulting T_c of both block copolymers had the same

values with the values at pH 7.4; although the PDMAEMA might not be in the protonated state, the significant effect of deprotonated COOH still weakened the tendency of neighboring PNIPAM block to collapse, forming aggregates when temperature increased above the T_c. Moreover, the decrease in the T_c of the block copolymers in comparison with PNIPAM macro-CTA could be caused by the presence of a neutral form of PDMAEMA. This leads to PDMAEMA being dehydrated at a high temperature and producing changes in hydrophilic-to-hydrophobic properties. Notably, at pH 7.4 and pH 9, the same T_c values were produced for different chain lengths of the PDMAEMA block, which was due to the strong interaction between PNIPAM and PDMAEMA that might eliminate the effect of PDMAEMA degree polymerization on T_c [13].

PSA analysis was conducted to get information about the size distribution and Z-average diameter of the aggregates. The trend of the Z-average diameter of the PNIPAM$_{21}$-*b*-PDMAEMA$_2$ at pH 5 is shown in Fig. 6(a). It was observed that the resulting Z-average diameter exhibited a similar trend compared to transmittance from UV-Vis spectroscopy. The result had shown that the size of micelles became bigger when temperature increased, as evidenced by the decrease in transmittance and an increase in the Z-average diameter (Fig. 6(a)). As displayed in Fig. 6(b), the particle diameter distribution shifted towards a larger diameter side as increasing

temperature. This might indicate that the block copolymer experienced self-assembly behavior to form micelles to minimize the contact from the hydrophobic groups with water in its surrounding environment. Increasing the temperature further may lead micelles to form clusters, and thus, large particle sizes were obtained.

It was also observed that there was a big difference between the resulting Z-average diameter of PNIPAM$_{21}$-*b*-PDMAEMA$_2$ at pH 5 and 9, in which the diameter of the Z-average at pH 9 was 846 nm while at pH 5 it was about 293 nm (Table 3). The possible reason was due to the differences in the shape of the micelles formed. It was known that at pH 5, the amine group in the PDMAEMA block was protonated, resulting in the positive charge that caused PDMAEMA to become more hydrophilic. Therefore when temperature increased, PDMAEMA tended to occupy the hydrophilic part as the shell of the micelles. The presence of PDMAEMA, which were positively charged on the shell of the micelles, caused an electric repulsion phenomenon that caused the particle to move apart from each other, and the micelles tended

Table 3. Z-average diameter of PNIPAM$_{21}$-*b*-PDMAEMA$_2$ at different pH

pH	Z-average diameter at 45 °C
5	293 nm
9	846 nm
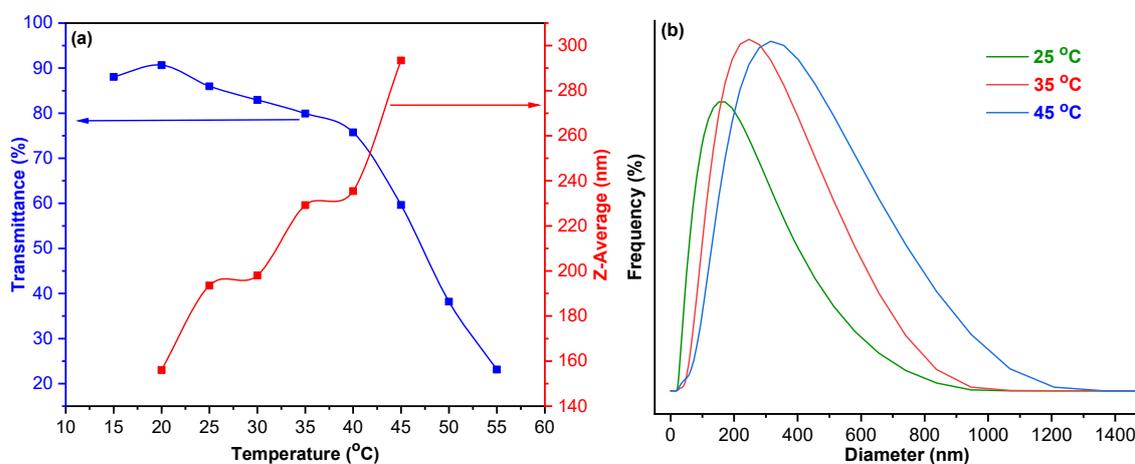
Fig 6. Thermo-responsive behavior and changes in Z-average of PNIPAM$_{21}$-*b*-PDMAEMA$_2$ at pH 5 (a). Distribution of diameter of the PNIPAM$_{21}$-*b*-PDMAEMA$_2$ at pH 5 (b)

to be stabilized from forming larger aggregate clusters. On the contrary, at pH 9 the PNIPAM block and PDMAEMA block would transform from hydrophilic to more hydrophobic when the temperature increased, and thus, they would occupy the core of the micelles since the shell of the micelles also preferred the hydrophobic interaction (Scheme 2). This could make the micelles unstable and form a cluster of micelles [33].

■ CONCLUSION

Block copolymers PNIPAM-*b*-PDMAEMA containing thermo- and pH-responsive properties have been synthesized via RAFT polymerization. FTIR and ¹H-NMR revealed the successful formation of PNIPAM-*b*-PDMAEMA. GPC confirmed the successful synthesis of block copolymers with well-controlled molecular weight as evidenced by narrow symmetrical molecular weight distribution with low polydispersity. The block copolymers showed micellization properties which were assigned to thermo- and pH-responsive behavior by exhibiting phase transition and increase of Z-average diameter upon heating. At pH 5, the longer the PDMAEMA chain would increase the T_c of the PNIPAM-*b*-PDMAEMA block copolymer, while at pH 7.4 and 9, T_c was not affected by the PDMAEMA chain length. Moreover, the synthesized block copolymers are open for new potential material in drug delivery systems.

■ AUTHOR CONTRIBUTIONS

Noverra Mardhatillah Nizardo designed the experiment, wrote, and revised the manuscript, Rida Hasna Fadhilah conducted the experiment and wrote the manuscript, Ivandini Tribidasari Anggraningrum wrote and revised the manuscript. All authors agreed to the final version of this manuscript.

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